REMARKS/ARGUMENTS

I. Status of the Claims

Following entry of the amendments herein, claims 46-49 are pending.

II. The Present Amendments

The amendments herein add no new matter.

The amendments to the specification update the specification by providing patent numbers corresponding to U.S. Serial Nos. 10/328,495 and 09/252,148 and to clarify references made to applications or WO publications in the specification. The specification has further been amended to reflect that the box symbols ("□") in these paragraphs adjacent to the abbreviation for molar ("M") were meant to be "μM," as evidenced by the IC50s provided in Table 1 wherein DCU (dicyclohexylurea – the penultimate compound found at page 7 of Table 1) is reported as having an IC50 of 0.09 ± 0.01 μM in mice. This micromolar value corresponds to a more exact valuation of the IC50 of 0.086 ± 0.014 □M found in paragraph [0074], which validates that these boxes are meant to be "μ". In paragraph [0065], the recitation "[1-14C]" has been corrected to read as "[1-^{14}C]" as recited in paragraph [0014]. Additionally, "(0.045-009 □Ci)" as set forth in paragraph [0065] as filed has been corrected to read "(0.045-009 μCi)" which is reflected in the second line of that paragraph. Similarly, the box symbol in front of the term "hydrolase" in paragraph [0074] corresponds to "ω-hydrolase," as found in the specification at paragraph [0078], line 33. The box symbols were deleted in a preliminary amendment filed on June 14, 2005. Applicants submit that the micromolar symbols and the omega symbol of the present amendment are both supported by the specification and a reading aid for the reader. Paragraph [0076] has been amended to reflect the IC50s found in Table 1 rather than referring to unpublished data. The amendments also correct minor typographical errors.

Applicants have canceled claims 14-45 without prejudice or disclaimer. In fact, during the interview, the undersigned advised Examiner Kwon that claims would be pursued in a continuation application to provide broader coverage than that found in the present claims and

that the present claims were being prosecuted solely to substantiate the lack of anticipation of the claimed invention over the cited art.

New claim 46 corresponds to previously presented claims 14 and 15 as set forth in the preliminary amendment dated June 14, 2005, with the exception that the variables X, W, Y, Z, R^2 and R^4 found in previously presented claim 15 have been limited to the species elected in the December 7, 2005, telephone conference between the Examiner and the undersigned and confirmed in the Applicants' Amendment dated June 13, 2006 (W = C; X and Y = N; Z = O and R^2/R^4 = H). Claim 47 references the compounds of Table 1 which correspond to the elected species. Claim 48 corresponds to previously presented claims 30 and 31 as found in the preliminary amendment of June 14, 2005, with the exception that the variables X, W, Y, Z, R^2 and R^4 found in claim 31 have been limited to the elected species noted above. Claim 49 sets forth the compounds of Table 1 which correspond to the elected species.

III. The January 2007, Interview

The undersigned thanks Examiner Kwon for the courtesy extended to him, Mr. Gerald Swiss and Ms. Traci Ropp during the personal interview conducted regarding this application on January 19, 2007. The interview summary provided by the Examiner correctly summarizes that the art of record and the proposed amendment to the claims made herein was discussed.

IV. The Rejections and Responses thereto

A. Rejections Under 35 U.S.C. §112, first paragraph

Claims 42-43 are rejected under 35 U.S.C. §112, first paragraph, for the reasons of record. While Applicants do not acquiesce to the rejection, it is now moot since the claims to which it applied have been canceled. Withdrawal of the rejection is respectfully requested.

Claims 14-18, 21-22, 30-34 and 37-38 are rejected under §112, first paragraph, for the reasons of record. Again, without acquiescing to the rejection, it is now moot as the now

presented claims obviate the basis of this rejection. Withdrawal of the rejection is respectfully requested.

B. Rejections Under 35 U.S.C. §102(b) and (e)

In the Office Action dated August 23, 2006 (the "Action"), the Examiner maintains the rejection of claims 14-18, 21-22, 30-34 and 37-38 under 35 U.S.C. § 102(b) as being anticipated by Ichihara et al., JP 07304755 ("Ichihara"), and claims 14-18, 21-23, 27-34 and 37-40 under § 102(e) as being anticipated by Blum et al., U.S. Patent No. 5,962,455 ("Blum"). As the claims to which these rejections were applied have been canceled, this rejection is moot. To expedite prosecution, however, Applicants address below and traverse the rejection in the context of now presented claims 46-49.

The Action acknowledges that both references are "silent about the functional characteristic of" the compounds they disclose in inhibiting soluble epoxide hydrolase, but asserts that "such property or characteristic [is deemed] to be inherent to the compounds disclosed by [the references] which read on the claimed structure compounds." Action, at page 11. Apparently, the Office Action is asserting that the compounds disclosed in Ichihara and Blum read on the "claimed structure compounds" and thereby have the functional characteristic of inhibiting soluble epoxide hydrolase ("sEH").

Applicants respectfully observe, however, that the claims under examination are not composition claims but rather are drawn to methods of decreasing blood pressure (claims 46 and 47) or reducing hypertension (claims 48 and 49) by administering therapeutically effective amounts of an inhibitor of soluble epoxide hydrolase. Thus, compounds which might otherwise fall within the genus of structures encompassed by the claims are not encompassed by the claimed methods unless they (1) are sEH inhibitors *and* (2) can be administered in therapeutically effective amounts.

The Action's position rests on the assumption that all compounds having the claimed structures - that is, all compounds containing a urea - inherently would also inhibit sEH, and would therefore be effective in treating hypertension It is not reasonable to assume,

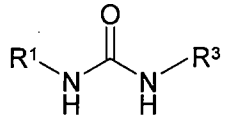
however, that compounds inherently possess the function of inhibiting sEH merely by the presence of a urea structure within their formula.

As an initial matter, Applicants respectfully note that that weak sEH inhibitors do not have an effect on hypertension. The specification states, in paragraph [0076], that "N-cyclohexyl-N'-ethylurea ... a weak sEH inhibitor (IC50 with mouse sEH = 51.7 ± 0.7 μM ...) ... had no effect on blood pressure." The paragraph further recites that compounds which are strong inhibitors of sEH do, in fact, lower blood pressure.[1] The specification concludes that these data demonstrate that reduced blood pressure *in vivo* correlates with strong sEH inhibition *in vitro*.

The apparent presumption in the Action that any urea based compound of the prior art that is taught as having anti-hypertensive activity is *de facto* acting as an sEH inhibitor is both factually and legally in error.

First, Applicants maintain that the logical corollary to the above assertion is that any compound exhibiting sEH inhibitory activity must exhibit anti-hypertensive activity as well. As noted above, however, the specification recites that N-cyclohexyl-N'-ethyl-urea, an sEH inhibitor (albeit having an IC50 of 51.7 ± 0.7 μM), fails to lower blood pressure. This evidence is clearly inconsistent with the assertion in the Office Action and its logical corollary.

Second, as observed during the interview, not all compounds of the structure:



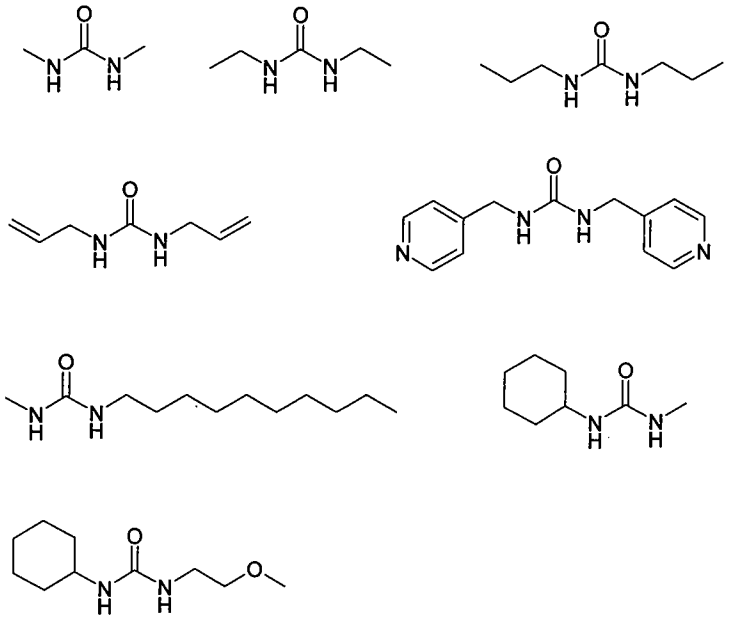
are inhibitors of sEH. The Examiner's attention is respectfully drawn to the Declaration of Dr. Hammock presented with the Amendment dated June 13, 2006 (the "First Hammock Declaration"). Dr. Hammock stated in paragraph 7 of the First Hammock Declaration that urea

[1] Paragraph [0074] states that dicyclohexyl urea (DCU) administered at 3 mg/kg demonstrated an antihypertensive effect by lowering blood pressure in the SHR by 22 ± 4 mm Hg six hours after treatment ($p < 0.01$) and that the blood pressure returned to baseline levels by 24 hours after dosing. The paragraph further states that N-cyclohexyl-N'dodecyl urea (CDU), when administered in a single dose, demonstrated an antihypertensive effect by lowering blood pressure in the SHR by 12 ± 2 mm Hg six hours after treatment and that the blood pressure returned to baseline levels by 24 hours after dosing.

DCU possesses an IC50 for mice/human sEH of 0.09/0.16 μM (90/160 nM), as per Table 1, whereas CDU possesses an IC50 for mice/human sEH of 0.05/0.10 μM (50/100 nM) as per Table 1. All values are ± 0.01.

($H_2NC(O)NH_2$) and simple 1,3-di-substituted ureas such as diethyl and dipropyl urea do not inhibit sEH.

Third, accompanying this amendment is a second declaration of Dr. Hammock (the "Second Hammock Declaration"). In this second Declaration, Dr. Hammock points out that the following ***representative*** urea based compounds do not inhibit by 50% the activity of sEH in hydrolyzing epoxides at a concentration of less than about 500 μM:



This data demonstrates that a compound does not inhibit sEH simply because it contains a urea and, more specifically, undercuts the premise of the Action's rejection that the compounds disclosed in the Ichihara and Blum references can be assumed to be inhibitors of sEH simply because they contain a urea.

Fourth, the rejection is also legally inadequate, as it does not meet the Examiner's burden of providing evidence or scientific reasoning to support a *prima facie* case of inherent anticipation. The entirety of Dr. Hammock's First Declaration was dismissed by the Action as opinion lacking any evidence. As noted above, however, Dr. Hammock stated in ¶7 of the First Hammock Declaration that urea, diethyl urea, and dipropyl urea do not inhibit sEH activity in the millimolar range. This statement is not of opinion but of fact, and was not addressed by the Office Action. For this reason alone, the rejection is in error and should be reconsidered.

Further, as pointed out in the January Interview, Dr. Hammock made statements regarding each of the specific compounds disclosed in the Ichihara and Blum based on the structure-activity relationships observed for over 2000 compounds. Dr. Hammock's sworn statements in the First Hammock Declaration were therefore not mere abstract opinions but factual statements based on extensive experimental evidence. The dismissal of these statements as mere opinion therefore on its face failed to give them appropriate weight and consideration.

Further, Dr. Hammock's First Declaration states that urea containing compounds having bulky and/or polar groups near the urea typically do not inhibit soluble epoxide hydrolase at physiologically relevant concentrations. As noted above, each of the claims at issue in the present application have, as primary limitations, the requirements that the method comprise administering to the patient a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase. Dr. Hammock's First Declaration not only calls into question whether the compounds identified by the Examiner would inhibit soluble epoxide hydrolase at all, but also establishes that the compounds of Blum and Ichihara could not be administered in a therapeutically effective amount because these compounds "will not significantly inhibit human sEH at physiologically relevant concentrations." As Dr. Hammock stated in the First Hammock Declaration:

> I have reviewed the structures of the compounds disclosed by Ichihara and the compounds disclosed by Blum. I disagree with the Action's contention that the compounds disclosed by either of these references would function to significantly inhibit sEH [*sic*, soluble epoxide hydrolase] (hereafter, "sEH") at physiologically relevant concentrations. (I put this qualification in since many otherwise inactive compounds are capable of inhibiting an enzyme's activity if present at concentrations beyond those that can be achieved *in vivo*.)

First Hammock Declaration at ¶5. Accordingly, Applicants submit that the Action has failed to present a proper *prima facie* case of anticipation, based on inherent properties, by Blum or by Ichihara. Moreover, the Action has not provided any evidence or reasoning to support its conclusion that either of the cited references discloses an inhibitor of soluble epoxide hydrolase or that the amount administered would be therapeutically effective as an inhibitor of soluble epoxide hydrolase.

It is well settled that the burden of establishing a *prima facie* case of anticipation resides with the Patent and Trademark Office. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785,788 (Fed. Cir. 1984) quoting *in re Warner*, 379 F.2d 1011, 1016, 154 USPQ 173, 177 (CCPA 1967). When the PTO shows sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not. *In re Spada*, 911 F.2d 705,708, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Before an applicant can be put to the burdensome task of proving that the subject matter of the prior art does not possess the characteristic relied upon by the PTO, however, the Examiner must provide some evidence or scientific reasoning to establish the reasonableness of the Examiner's belief that the functional limitation is an inherent characteristic of the prior art. *Ex parte Skinner*, 2 USPQ2d 1788, 1789 (Bd. Pat. App. 1986). In this case the Action has failed to provide any evidence or scientific reasoning in support of the belief that the methods of Ichihara and Blum disclose a method of reducing blood pressure by administering a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase (*e.g.* as per claim 14) or a method of reducing hypertension by administering a therapeutically effective amount of an inhibitor of soluble epoxide hydrolase (*e.g.*, as per claim 30).

Indeed, not only has the Action failed to provide evidence or scientific reasoning to support its conclusion, the Second Declaration of Dr. Bruce Hammock identifies a number of urea-based compounds which are not sEH inhibitors and, accordingly, are not covered by the claim language that the compounds of the disclosed structure must inhibit sEH in therapeutically effective amounts (e.g., at physiologically relevant concentrations). Thus, Applicants maintain that, even if the Action presented a proper *prima facie* case of inherent anticipation, which Applicants maintain it did not, it has been rebutted by the evidence presented in the Second Hammock Declaration.

Reconsideration and withdrawal of the rejection are respectfully requested.

C Rejection Under 35 U.S.C. §103(a)

Claims 26 and 41 stand rejected under 35 U.S.C. §103(a) over Blum, above, in view of the Merck Manual ("Hypertension, Fifteenth Edition, 1987). This rejection is both traversed and obviated.

To the extent the rejection is predicated on the presumption that the compounds disclosed in Blum would inherently reduce hypertension by inhibiting sEH, the rejection must be reconsidered and withdrawn in light of the discussion presented in the preceding section.

Further, the rejection is obviated as Claims 26 and 41 have been canceled and no new claims corresponding thereto have been introduced. Reconsideration and withdrawal of this rejection is therefore appropriate, and requested.

D. Prior Rejection under 35 U.S.C. §101

Claims 30-34 as previously presented were rejected under 35 U.S.C. §101 over claims 1-5 of U.S. Patent No. 6,531,506 (the "'506 patent") in the Office Action dated December 29, 2005. In response thereto, Applicants amended claim 30 to recite that the "inhibitor inhibits by 50% the activity of sEH in hydrolyzing epoxides at a concentration of less than about 500 μM" and then argued that this recitation differentiated over claims 1-5 of the '506 patent. Upon review and for the sake of good order, Applicants note that the specification recites at page 23, paragraphs [0039] and [0040], that preferred compounds inhibit sEH activity by 50% at a concentration of less than about 500 μM.

As the claims of the '506 patent are read in view of the specification, Applicants are uncertain as to whether such a recitation in claim 30 distinguishes over claims 1-5 of the '506 patent. Accordingly, claim 30 has been canceled and claims 46-49 presented which distinguish from claims 1-5 of the '506 patent under 35 U.S.C. §101.

E. Double Patenting Rejection

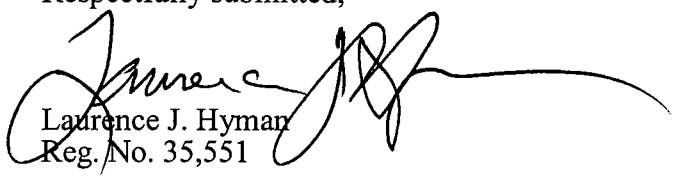
Previously pending claims 14-18, 21-23, 26-34, and 37-41 were rejected for double patenting under U.S. Patent No. 6,531,506 and further in view of the Merck Manual. To the extent that the rejection might apply to the claims as now presented, it will be addressed following the indication of allowable subject matter.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, he is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,



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